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EXAMINER	
HOWARD, ZACHARY C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,090	FERGUSON, DUNCAN C.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9,13,34-38 and 55-86* is/are pending in the application.

4a) Of the above claim(s) *5,9,13,34-38,62-69,73-80 and 86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,55-58,61,70-72 and 81-85* is/are rejected.

7)☒ Claim(s) *2,59 and 60* is/are objected to.

8)☒ Claim(s) *1-5,9,13,34-38 and 55-86* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/3/07;10/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence Alignments #1 and #2*.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 10/7/08 has been entered in full. Claims 6-8, 10-12, 14-33, 39-54 are canceled. Claims 4, 5, 13, 34 and 37 are amended. New claims 55-86 are added.

Claims 1-5, 9, 13, 34-38 and 55-86 are pending.

Election/Restrictions

New claims 55-85 belong to Group I as set forth at pg 2 of the 9/15/08 Office Action. New claim 86 is directed to an invention not claimed previously, herewith set forth as Group VIII, drawn to a method of making an antibody comprising immunizing an animal with a polypeptide. This is a distinct method of use of the product of Group I, and does not relate to a single general inventive concept under PCT Rule 13.1 for the reasons set forth previously for Groups I-VII, and maintained herein in response to Applicant's claim amendments (see below).

Applicant's election with traverse of Group I, claims 1-5, 9, 13, 37, 38 and 55-85, in the reply filed on 10/7/08 is acknowledged.

The traversal is on the ground(s) that "the inventions of Groups I-VII can be readily evaluated in one search without placing undue burden on the Examiner" (pg 1).

This is not found persuasive because search burden is not part of the criteria for restriction of a 371 application under 35 U.S.C. 121 and 372. Instead, the inventions listed as Groups I-VII were held to not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding technical feature (see page 3 of the 9/15/08 Office Action).

Applicant further states that "SEQ ID NO: 1 is the amino acid sequence of the feline thyrotropin β-subunit, while SEQ ID NO: 4 is the amino acid sequence of feline thyrotropin α-subunit ... the Examiner's assertion that the porcine thyrotropin α-subunit represented by Accession P0129 "is identical to a mutated variant of SEQ ID NO: 1" (page 3, Restriction Requirement mailed September 15, 2008) is incorrect" (pg 2).

This is found to be persuasive. The first sentence of the referenced paragraph correctly referred to an "isolated feline thyrotropin α-subunit polypeptide comprising at least 80% identity to SEQ ID NO: 4", but incorrectly referred to SEQ ID NO: 1 in several subsequent sentences. For the record, a corrected paragraph is presented here:

> Specifically, Group I encompasses an isolated feline thyrotropin α-subunit polypeptide comprising at least 80% identity to SEQ ID NO: 4. Thus, claim 5 encompasses variants of SEQ ID NO: 4 with or more amino acid changes to SEQ ID NO: 4, including mutated variants. The recitation of "feline" as a descriptor of the polypeptide is not limiting because there is nothing to distinguish a mutated variant of SEQ ID NO: 4 from a variant of SEQ ID NO: 4 from another species. For example, the prior art teaches a porcine sequence with 96.8% similarity to the feline sequence of SEQ ID NO: 4 (see the record for Accession P0129 in the NCBI GenBank Protein Database, created 1986, 3 pages as printed). An alignment of the two sequences is attached to this Office Action as Sequence Alignment #1, which shows a difference of four amino acids between the two sequences. This naturally-occurring sequence is identical to a mutated variant of SEQ ID NO: 4 that is encompassed by the instant claims. As such, the technical feature linking the inventions of group I-VII does not constitute a special technical feature as defined by PCT rule 13.2, as it does not define a contribution over the prior art. [changes indicated by underlining]

Thus, in spite of the typographical errors, the cited art was properly encompassed by the α-subunit recited in the claims of Group I, and the technical feature linking the inventions of Groups I-VII was properly held not to constitute a special technical feature as defined by PCT Rule 13.2.

In the 10/7/08 response, Applicant has amended the claims such that the cited art (the record for Accession P0129) is no longer encompassed by the claims of Group I. However, as set forth previously the "technical feature linking group I-VII [now I-VIII] appear to be that they all relate to polypeptides related by sequence identity to feline α- or β-subunit". Prior art is cited below (see "Claim Rejections - 35 U.S.C. 102(b)") that anticipates claims of Group I directed to the β-subunit. Thus, it is maintained that the technical feature linking the inventions of Groups I-VIII does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art. As the change in cited prior art showing lack of special technical feature was necessitated by Applicant's amendment to the claims, the requirement is still deemed proper and is therefore made FINAL.

Claims 34-36 and 86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/7/08.

Applicant further states that "[p]ursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996, (1184 O.G.86), the withdrawal of the restriction requirement as it relates to method claims 34-36 (Group V) and the rejoinder and examination of claims 34-36 and 90 [sic] is respectfully requested upon the identification of allowable subject matter within the claims of elected Group I" (pg 1) [it is believed that Applicant intends to refer to claim 86, as there is currently no claim 90].

This is found to be persuasive. The following statement regarding rejoinder was inadvertently left out of the restriction requirement mailed 9/15/08:

> The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant's election of the species of "isolated thyrotropin β-subunit" in the reply filed on 10/7/08 is acknowledged.

Applicant submits that claims 1-4, 13, 37, 38 and 55-89 read on elected species I and that claim 9 is generic to the elected species.

This is found to be persuasive in part. Claims 1-4, 55-60 and 81-84 are directed to the elected species, and claims 61, 70-72 and 85 are directed to a generic polypeptide encompassing the elected species (isolated thyrotropin β-subunit). However, claims 9, 13, 37, 38, 62-69 and 73-80 are related solely to polypeptides comprising both thyrotropin subunits (α and β), which is a non-elected species.

Claims 5, 9, 13, 37, 38, 62-69 and 73-80 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. It is noted that claims directed to the nonelected species will be rejoined if all claims directed to the elected species are indicated as allowable.

Claims 1-4, 55-61, 70-72 and 81-85 are under consideration, as they read upon the elected species.

Specification

The disclosure is objected to because of the following informalities:

(1) The title of the invention ("DNA SEQUENCE AND EXPRESSED RECOMBINANT GLYCOPROTEINS RELATED TO FELINE THYROTROPIN") is not descriptive because no claims are directed to DNA sequences. A new title is required that is clearly indicative of the claimed invention. The following title is suggested: "RECOMBINANT GLYCOPROTEINS RELATED TO FELINE THYROTROPIN".

(2) On page 40, it is stated that, "The sequence showed 99% homology with tiger (Panthera tigris) common alpha subunit (Genbank accession number AF354939)." However, this statement appears in Example 2, which is titled "Cloning and sequencing of feline thyrotropin β-subunit". Thus, it appears that the statement applies to Example 1 (concerning the cloning of the feline α-subunit) rather than Example 2.

(3) On page 40, it is further stated that, "The feline TSHβ was different from canine TSHβ by 5 amino acids, equine TSHβ by 4 amino acids, and human TSHβ by 15 amino acids". However, Rayalam et al #2 (2006, Domestic Animal Endocrinology. 30: 203-217; cited on page 4 of the 1/3/07 IDS) teaches that the "projected amino acid homology of the secreted feline β-subunit was (amino acids, %): dog (111, 94%), cattle (107, 90.5%), horse (110, 93.2%) and human (104, 88%)(Fig. 6)" (pg 208). Thus, in contrast to the statement in the specification, feline TSHβ is different from canine TSHβ by 7 amino acids, equine TSHβ by 8 amino acids, and human TSHβ by 14 amino acids.

(3) The sentence ending on line 7 of page 50 is missing a period.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 55-58, 61, 70-72 and 81-85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated feline thyrotropin β-subunit polypeptide comprising SEQ ID NO: 1 (including SEQ ID NO: 2), or isolated naturally-occurring canine, equine, cattle and human thyrotropin β-subunit polypeptides, does not reasonably provide enablement for an isolated feline thyrotropin β-subunit polypeptide comprising an amino acid sequence with at least 80% identity to SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a genus of isolated polypeptide variants related to a feline thyrotropin β-subunit polypeptide of SEQ ID NO: 1 (without signal sequence) or SEQ ID NO: 2 (with signal sequence). Thyrotropin is a mammalian heterodimeric protein consisting of two subunits (α and β). The β-subunit is specific to thyrotropin; the α-subunit is shared with several other heterodimeric proteins.

The specification teaches the following working examples in support of the claimed invention. Examples 1 and 2 (pg 39-40) teach the cloning and sequencing of the genes encoding feline thyrotropin α- and β-subunits (respectively). Example 3 (pg

41) teaches construction of a "yoked" fusion protein comprising the two subunits linked by a human chorionic gonadotropin C terminal peptide (CTP). Example 4 (pg 41-42) teaches baculovirus expression systems for the two subunits and the fusion protein. Example 5 (pg 43) describes expression of the two subunits and the fusion protein in three different cell systems. Examples 6 (pg 44) and 8(pg 46-48) describe immunological purification and detection of the proteins using an included FLAG epitope tag. Example 7 (pg 45-46) is labeled "prophetic example" and describes preparation of monoclonal antibodies against the fusion protein. Example 9 (pg 48-50) describes two assays to determine the biological activity of the fusion proteins. The first assay is a cAMP production assay using JP09 cells (CHO cells stably expressing the human TSH receptor). The specification reports that "[b]oth fTSH α/β heterodimer and yfTSH were biologically active in terms of cAMP production. fTSH heterodimer at 100 ng concentration produced 25 pmol/ml of cAMP where as yfTSH at the same concentration produced 70 pmol/ml. See the results presented in FIG. 6a" (pg 49). The second assay is a binding assay using the JP09 cells radioiodionated bovine TSH. The working examples presented in the specification are supported by two post-filing date publications (Rayalam et al #1, 2006. Domestic Animal Endocrinology. 30: 185-202; Rayalam et al #2, 2006. Domestic Animal Endocrinology. 30: 203-217; each cited on page 4 of the 1/3/07 IDS). Rayalam et al #1 teaches that "the heterodimeric and yoked forms of fTSH were able to inhibit the binding of ^{125}I-bTSH to the hTSH receptor in JP09 cells but with different affinities" (pg 195).

The recitation of "feline" in the claims does not structurally distinguish mutated variants of SEQ ID NO: 1 from identical sequences found in other animal species; therefore, the claims are interpreted broadly to encompass any polypeptide with the recited structure. As taught by Rayalam et al #2, 2006 (cited above), the "projected amino acid homology of the secreted feline β-subunit was (amino acids, %): dog (111, 94%), cattle (107, 90.5%), horse (110, 93.2%) and human (104, 88%)(Fig. 6)" (pg 208). As such, the instant claims encompass the naturally-occurring canine, equine, cattle and human TSHβ sequences known in the relevant art. Thus, the teachings of the specification and the relevant art enable the skilled artisan to make and use an isolated

feline thyrotropin β-subunit polypeptide comprising SEQ ID NO: 1, an isolated naturally-occurring canine, equine, cattle and human thyrotropin β-subunit polypeptides.

However, the claims also encompass non-naturally occurring variants of mammalian thyrotropin β-subunit polypeptides in which one or more amino acids of SEQ ID NO: 1 are substituted, deleted, and/or inserted. Claim 1 recites a polypeptide that comprises an amino acid sequence with at least 80% similar to SEQ ID NO: 1 (the sequence of wildtype feline β-subunit without signal sequence). SEQ ID NO: 1 is 118 amino acids in length; thus the genus of variants with at least 80% similarity to SEQ ID NO: 1 includes up to 23 combined amino acid changes. SEQ ID NO: 2 is 138 amino acids in length and fully comprises SEQ ID NO: 1 and a signal sequence.

None of the claims include the limitation that the polypeptide variants exhibit a characteristic of the parent polypeptide of SEQ ID NO: 1, such as (when bound to a feline α-subunit) stimulating cAMP production in cells expressing the TSH receptor. Thus, both functional and non-functional mutated variants of SEQ ID NO: 1 are encompassed by the claims. Expected performance parameters of any of the possible variants of SEQ ID NO: 1 are limited to naturally-occurring sequences from other mammalian species that fall within the claimed genus. The specification has not provided a working example of the use of a non-naturally occurring variant of SEQ ID NO: 1, or sufficient guidance to enable one of skill in the art to make and use such a variant. The specification has failed to teach which amino acids of SEQ ID NO: 1 could be modified to produce a polypeptide not identical to SEQ ID NO: 1 that retains a characteristic of the parent polypeptide, e.g., (when bound to a feline α-subunit) stimulating cAMP production in cells expressing the TSH receptor.

Applicant has not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between SEQ ID NO: 1 and non-naturally occurring variants of said protein. If a variant of SEQ ID NO: 1 is to have a structure and function similar to SEQ ID NO: 1, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 1. Conversely, if

a protein variant of SEQ ID NO: 1 need not have a disclosed property; the specification has failed to teach how to use such a variant.

Applicants do not identify any specific residues or regions of SEQ ID NO: 1 that are necessary for the activity of the protein. Furthermore, it is unpredictable whether or not the differences present in other naturally-occurring mammalian sequences can be used to predict changes that can be made to the feline sequence. A single amino acid change can drastically affect protein functionality if it occurs in a critical residue; thus, making a change based on another sequence may require additional compensatory changes elsewhere in the sequence. As noted in Ferrer-Costa (2007. J Mol Biol. 365: 249-256), non-human sequences may contain residues that are disease-associated in humans, but which are not disease-associated in the non-human animal: these changes are explained by compensatory changes elsewhere in the protein (see Abstract).

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change, and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al*. (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133].

To put the situation in perspective, the number of possible amino acid sequences that are 100 amino acids in length is 20^{100} (approx. 10^{130}). The number of possible amino acid sequences that are of a given % identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence (X = 19 for a polypeptide sequence), L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For example, for a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate

term of the formula) is approximately 6 x 10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1 x 10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where n<<L. Using this formula to approximate N in this example gives a value of 1.7 x 10^{26}.

In the present case, the reference amino acid sequence SEQ ID NO: 1 is 118 amino acids long. A sequence that is at least 80% identical to SEQ ID NO: 1 tolerates up to 23 amino acid changes. Therefore, the total number of possible amino acid sequences that are at least 80% identical to SEQ ID NO: 1 is about 4.5 x 10^{54} ((19^{23} * 118^{23})/23!). Thus, while limiting the scope of potential sequences to those that are at least 80% identical to a reference sequence greatly reduces the number of potential sequences to test (as compared to having no structural limitation at all), it does not do so in any meaningful way. Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which have the activity of SEQ ID NO: 1. Even considering a much narrower genus recited in the claims, such as "at least 90% identical to SEQ ID NO: 1" (which tolerates up to 11 amino acid changes in any combination (0.90 x 118 = 106.2), the total number of possible amino acid sequences is still about 1.8 x 10^{29} (19^{11} * 118^{11})/11!), which is more than a billion billions. Such a genus is still so vast that it would clearly require undue experimentation for the skilled artisan to make and test even a representative number of species from the genus. Even narrower claims, such as claim 58, which recites "at least 99% identity to SEQ ID NO: 1" (which only tolerates a single amino acid change in SEQ ID NO: 1), lack enablement in absence of a functional limitation. This is because the art teaches that even single amino acid changes can drastically alter protein functionality and the specification does not teach how to use non-functional variants of SEQ ID NO: 1.

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features

are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1, 3, 4, 55-58, 61, 70-72 and 81-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant is claiming and what Applicant has possession of. The claims are genus claims directed to variant polypeptides; the genus is highly variant because a significant number of structural differences between members are permitted. For example, claim 1 is drawn to any polypeptide comprising an amino acid sequence with at least 80% similar to SEQ ID NO: 1. Therefore, the claim encompasses polypeptides comprising sequences with up to 20% variation with respect to the polypeptide of SEQ ID NO: 1. The claims do not require that the polypeptides possess any particular conserved structure or function. The claims only require the claimed polypeptides share some structural similarity to the isolated polypeptide of SEQ ID NO: 1. Thus, the claims are drawn to a genus of polypeptides defined only by sequence similarity. The instant specification fails to describe the entire genus of polypeptides that are encompassed by each of these claims. From the specification, it is clear that Applicant has possession of an isolated thyrotropin β-subunit polypeptides of SEQ ID NO: 1 (without signal sequence) and SEQ ID NO: 2 (with signal sequence), and isolated naturally-occurring canine, equine, cattle and human thyrotropin β-subunit polypeptides. The specification

fails to describe or teach any non-naturally occurring polypeptide which differs from the sequence of SEQ ID NO: 1 and retains the characteristics of the parent polypeptide. The claims, however, are not limited to a polypeptide of SEQ ID NO: 1 or another naturally-occurring mammalian thyrotropin β-subunit polypeptide.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated feline thyrotropin β-subunit polypeptide comprising SEQ ID NO: 1 (including SEQ ID NO: 2), and isolated naturally-occurring canine, equine, cattle and human thyrotropin β-subunit polypeptides, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claims 82 and 84 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

New claim 82 is directed to a kit comprising the feline thyrotropin β-subunit polypeptide of claim 1 and a thyroid radiosensitizing agent. The instant specification as originally filed does not teach such kits. The instant specification teaches use of

thyrotropin as a "thyroid radiosensitizing agent": "[a] preferred embodiment of the method of treating feline hyperthyroidism involves the use of feline thyrotropin, as a heterodimer or yoked polypeptide, as a thyroid radiosensitizing agent. Feline thyrotropin in this role acts to stimulate activity of the thyroid, which in turn renders the thyroid more susceptible to ablation by radioiodide" (¶ 76 of the published application). However, the term "thyroid radiosensitizing agent" is broader in scope than just thyrotropin. The specification does not any other radiosensitizing agents, or kits comprising such. Thus, while the specification as originally filed teaches kits comprising thyrotropin, the specification does not teach kits comprising thyrotropin and a radiosensitizing agent.

New claim 84 is directed to a "composition comprising the feline thyrotropin β-subunit polypeptide of claim 1 and an adjuvant". The specification as originally filed does not teach such compositions. The term "adjuvant" is used three times in the specification, solely in Example 7. In Example 7, the "yoked polypeptide is emulsified in Complete Freund's Adjuvant"; this emulsion is referred to twice in this example. This specific example is different in scope than claim 84; specifically, the "yoked polypeptide" of Example 7 is much narrower in scope than the polypeptide encompassed by claim 84 and "Complete Freund's Adjuvant" is much narrower in scope than "adjuvant". The third reference is to "without adjuvant" (¶ 114 of the published application). Thus, while the specification as originally filed teaches a specific emulsion comprising a specific yoked polypeptide and a specific adjuvant (Complete Freund's), there is no teaching directed to the broader composition recited in claim 84.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 55, 56, 61, 70, 72 and 81-85 are rejected under 35 U.S.C. 102(b) as being anticipated by Yang et al, 2000 (Domestic Animal Endocrinology. 18: 363-378; cited on page 7 of the IDS filed 10/12/07).

Claim 1 is directed to "an isolated feline thyrotropin β-subunit polypeptide comprising an amino acid sequence with at least 80% identity to SEQ ID NO: 1". The recitation of "feline" does not structurally distinguish mutated variants of SEQ ID NO: 1 from identical sequences found in other animal species; therefore, the claim is interpreted broadly as simply a name for any polypeptide with the recited structure.

Yang teaches the cloning of canine thyrotropin β-subunit gene (see Abstract). Yang teaches that the DNA sequence has the same sequence as shown in the record for Genbank Accession #U51644. The record for U51644 has been submitted by Applicant with the IDS filed 1/3/07 (see page 3). This record shows a translated protein sequence identical to that found in the record for Accession P54828, NCBI GenBank Protein Database, created Oct 1, 1996 (cited on page 5 of the IDS filed 10/12/07). The record for Accession Number P54828 teaches a protein of 138 amino acids that is described as a thyrotropin β-subunit from "Canis lupus familiaris (dog)". Sequence Alignment #1 (attached to this Office Action) shows that residues 21-138 of the protein taught by P54828 share 94.2% identity with instant SEQ ID NO: 1. Therefore, Yang et al teach a thyrotropin subunit polypeptide that comprises an amino acid sequence with at least 80% sequence identity to SEQ ID NO: 1, and therefore the teachings of Yang et al anticipate instant claim 1.

Claim 3 depends from claim 1 and limits the polypeptide of claim 1 to further comprising a signal sequence. The record for P54828 teaches that this polypeptide comprises a signal sequence (residues 1-20). Therefore, the teachings of Yang et al also anticipate instant claim 3.

Claim 4 depends from claim 3 and limits the polypeptide to one comprising an amino acid sequence with at least 80% identity to SEQ ID NO: 2. Sequence Alignment #2 (attached to this Office Action) shows that the protein taught by P54828 share 94.5% identity with instant SEQ ID NO: 2. Therefore, Yang et al teach a thyrotropin subunit polypeptide that comprises an amino acid sequence with at least 80% sequence identity to SEQ ID NO: 2, and therefore the teachings of Yang et al also anticipate instant claim 4.

Claims 55 and 56 each depend from claim 1 and limit the polypeptide to one wherein the amino acid sequence comprises at least 85% (claim 55) or 90% identity (claim 56) to SEQ ID NO: 1. The teachings of Yang et al anticipate claims 55 and 56 for the same reasons as for claim 1 (described above).

Claim 61 is directed to "[a]n isolated thyrotropin comprising the feline thyrotropin β-subunit polypeptide of claim 1". The term "thyrotropin" encompasses a thyrotropin β-subunit as recited in claim 1. Therefore, claim 61 is anticipated by the teachings of Yang et al for the same reasons as for claim 1 (described above).

Claim 70 is directed to a polypeptide comprising an amino acid sequence with at least 80% identity to SEQ ID NO: 1. As described above for claim 1, Yang et al teaches a thyrotropin subunit polypeptide that comprises an amino acid sequence with at least 80% sequence identity to SEQ ID NO: 1, and therefore the teachings of Yang et al also anticipate instant claim 70.

Claim 72 depends from claim 70 and limits the polypeptide to one comprising an amino acid sequence with at least 80% identity to SEQ ID NO: 2. As described above for claim 4, the Yang et al teach a thyrotropin subunit polypeptide that comprises an amino acid sequence with at least 80% sequence identity to SEQ ID NO: 2, and therefore the teachings of Yang et al also anticipate instant claim 72.

Claim 81 encompasses a "kit" comprising a polypeptide of claim 1 and "packaging materials". The instant specification does not provide a limiting definition of the term "kit" or "packaging materials". As such, a "kit" broadly encompasses any combination of the elements recited in the claim; specifically, "the feline thyrotropin β-subunit polypeptide of claim 1" and "packaging materials". Furthermore, the term "packaging materials" broadly encompasses any sort of containing structure. Yang et al teach "recombinant canine TSHβ" analyzed by Western blot (Figure 5, pg 372). The gel and membrane used in this Western blot analysis constitutes "packaging materials". Thus, Yang et al teach a "kit" comprising a polypeptide of claim 1 and "packaging materials". Therefore, the teachings of Yang et al anticipate claim 81.

Claim 82 encompasses a "kit" comprising a polypeptide of claim 1 and a "thyroid radiosensitizing agent". The instant specification teaches that thyrotropin itself is a

"thyroid radiosensitizing agent": "[a] preferred embodiment of the method of treating feline hyperthyroidism involves the use of feline thyrotropin, as a heterodimer or yoked polypeptide, as a thyroid radiosensitizing agent. Feline thyrotropin in this role acts to stimulate activity of the thyroid, which in turn renders the thyroid more susceptible to ablation by radioiodide" (¶ 76 of the published application). Thus, the polypeptide of claim 1 is itself encompassed by the term "thyroid radiosensitizing agent". Therefore, claim 82 is anticipated by Yang et al for the same reasons as claim 81.

Claim 83 encompasses a "kit" comprising the polypeptide of claim 1 and an anti-thyrotropin antibody. Yang et al teach "recombinant canine TSHβ" analyzed by Western blot (Figure 5, pg 372) using "polyclonal rabbit antiserum previously prepared against the native canine TSH" (pg 372). Thus, Yang et al teach a combination of a polypeptide of claim 1 and an anti-thyrotropin antibody. Therefore, the teachings of Yang et al also anticipate claim 83.

Claim 84 encompasses a "composition" comprising the polypeptide of claim 1 and an "adjuvant". The term "adjuvant" is not defined in the instant specification, and as such broadly encompasses any agent that modifies the effect of another agent. Therefore, the term "adjuvant" encompasses an antibody that binds to (and thus modifies) a polypeptide of claim 1. As described above, Yang et al teach "recombinant canine TSHβ" analyzed by Western blot (Figure 5, pg 372) using "polyclonal rabbit antiserum previously prepared against the native canine TSH" (pg 372). The protein bound by antibody in the Western blot meets the definition of a "composition". Therefore, the teachings of Yang et al anticipate claim 84.

Claim 85 encompasses a composition comprising a polypeptide of claim 70. As described above, Yang et al teach a polypeptide of claim 70 for the same reasons as claim 1. Furthermore, as described above for claim 84, Yang et al teach a composition comprising a polypeptide of claim 1. Therefore, claim 85 is anticipated by Yang et al for the same reasons as claim 84.

Conclusion

Claims 2, 59 and 60 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Z. C. H./
Examiner, Art Unit 1646

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